REMARKS

Claims 1-7, 9-18, 21-26, 28-40 and 42-54 are pending in the instant application. Claims 1-7, 9-18, 21-26, 28-40 and 42-54 have been rejected. Claims 1-7, 9-18, 21-26, 28-40 and 42-54 have been canceled without prejudice. New claims 55-67 have been added. Support for these amendments is provided in claims 44-54, now canceled and throughout the specification for example at page 2, lines 15-25; page 4, lines 1-4; page 6, lines 6-18; page 6, line 26 through page 7, line 9; page 7, lines 20-30 and page 8, lines 19-24. Thus, no new matter is added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims 1-7, 9-18, 21-26, 28-38, 44-45, 47-48 and 51-53 and 38 under 35 U.S.C. 112, second paragraph

The Examiner has maintained the rejection of claims 14, 33 and 38 under 35 U.S.C. 112, second paragraph. The Examiner suggests that amendments to the claims in the response filed September 7, 2004 are not sufficient to overcome the indefinite nature of the claims because the meaning of the term "respectively" is still unclear.

Further the Examiner has rejected claims 1-7, 9-18, 21-26, 28-37, 44-45, 47-48 and 51-53 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner suggests that it is unclear in the recitation in claims 1 and 21 of "a non-infectious nucleic acid which upon administration to the animal encodes a recombinant antibody" how such a nucleic acid could only encode the antibody upon administration. Further, the Examiner suggests that it is unclear if it encodes the antibody during the process of administering the nucleic acid, or if it encodes the antibody after administration.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have canceled without prejudice pending claims 1-7, 9-18, 21-26, 28-40 and 42-54. Subject matter of these claims is re-presented in new claims 55-67 which do not contain either of the phrases which the Examiner suggested to be indefinite.

Withdrawal of these rejections under 35 U.S.C. 112, second paragraph is therefore respectfully requested.

II. Rejection of Claims 1-7, 9-18, 21-26, 28-40 and 42-54 under 35 U.S.C. 112, first paragraph

The rejection of claims 1-7, 9-18, 21-26, 28-40 and 42-54 under 35 U.S.C. 112, first paragraph, has been maintained. The Examiner has acknowledged the specification to be enabling for a composition for protection of a fish against viral haemorrhagic septicaemia virus (VHSH)

comprising a non-infectious DNA nucleic acid construct encoding the single chain antibody 3F1H10 that recognizes VHSV, the DNA sequence for the antibody listed on pages 9-10 of the specification and which comprises substitutions of asparagine 35 with threonine and lysine 64 with threonine and is linked at the 5′ end to the secretion signal of transforming growth factor beta, and which sequence is operably linked to the CMV promoter and a polyA tail for protecting a fish against VHSV infection, and vaccines comprising said compositions and method of providing prophylactic treatment of fish against VHSV by the administration of these compositions, by injection into the epaxial muscles below the dorsal fin, which compositions transform cells of the muscle tissue local to the injection site and produce secreted 3F1H10 antibodies, thereby producing protection against VHSV. However, the Examiner suggests that the specification does not reasonably provide enablement for any nucleic acid construct encoding any antibody, any secretion sequence, any promoter sequence, any form of administration, any form of composition, treatment of any animal, or any form of treatment for any disease-causing agent.

Applicants respectfully traverse this rejection.

The inventors of the instant patent application are the first to show that passive, protective immunity to an infectious pathogen in vertebrates can be established by administration of genes encoding pathogen specific single chain antibodies. In an earnest effort to advance the prosecution of this case, Applicants have cancelled pending claims 1-54 and re-presented the subject matter in new claims 55-67 which are drawn to methods for passive immunisation of an animal against a disease-causing agent by administering to an animal non-infectious eukaryotic expression vector nucleic acid construct comprising a DNA sequence encoding a recombinant antibody molecule derived from an antibody raised against the disease-causing agent. Support for these claims is provided in originally filed claims 1-54 and in teachings throughout the specification. See e.g. at page 2, lines 15-25; page 4, lines 1-4; page 6, lines 6-18, page 6, line 26 through page 7, line 9; page 7, lines 20-30 and page 8, lines 19-24. No new matter is added by these amendments.

> 35 U.S.C. §112, first paragraph, provides, in part: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same,...

To fulfil the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that as of the filing date the inventor had possession of the claimed invention.

The present inventors, at the day of invention, were in possession of the following i) technology of making functionally active recombinant antibodies (against any antigen); ii) technology of constructing expression vectors for in vivo expression; iii) knowledge of a variety of effective (in different species) promoter and secretion signal peptide sequences; and iv) knowledge of the effective routes of administration of eukaryotic expression vectors to animals allowing obtaining expression of the encoded protein in vivo.

Further, Applicants have described in detail in the instant specification an example of advantageous use of the disclosed technology for the establishment of passive, protective immunity in an exemplary animal species to an exemplary type of pathogen. Applicants have also provided guidance to which secreting sequences are more preferable to use. Further, Applicants have indicated in the specification that experimentation with respect to choice of

an expression vector can be avoided as a gene of interest can be inserted and in vivo expression obtained with any commercially available vector using known technologies. Applicants, at the time of filing the application, also provided a list of well known pathogens, antibodies against which have been disclosed in the prior art, and therefore it would not demand undue experimentation to make a recombinant derivate thereof. Further, Applicants have provided a declaration by inventor Dr. Niels Lorenzen, which states that a construct of the present invention has been successfully used in an unrelated vertebrate species to establish a protective immunity against a toxin.

Mice have been the most extensively used animal model in human medical science during the last decades and since the late 1990´s the usefulness of disease models in fish has become apparent. See I. Zon: Zebrafish: a new model for human disease *Genome Research* 1999 Feb;9(2):99-100, a copy of which is provided herewith.

Thus, Applicants, at the time of filing the instant application were clearly in possession of a method for passive immunization of an animal against a disease-causing agent by administering to an animal non-infectious eukaryotic expression vector nucleic acid construct

comprising a DNA sequence encoding a recombinant antibody molecule derived from an antibody raised against the disease-causing agent as claimed.

Applicants are also providing herewith two recent papers reporting results with mice and sheep confirming the general applied potential of the instant invention in small and larger mammalian species. In particular, Applicants are providing herewith a copy of T. E. Tjelle et al. 2004: Monoclonal Antibodies Produced by Muscle after Plasmid Injection and Electroporation. *Molecular Therapy* 9 (3) 328-336 and N. Perez et al. 2004: Regulatable systemic production of monoclonal antibodies by *in vivo* muscle electroporation. *Genetical Vaccines Therapy*. 2004 Mar 23;2(1):2.

Thus, the applied animal model disclosed in detail in the instant specification, which was used in proof of concept experiments, is clearly predictive of results in general in other animals (including humans). These experiments, coupled with detailed teachings in the specification of other disease causing agents, additional expression vectors, and other animals in which passive immunity can be established in accordance with the present invention provide sufficient detail so that one skilled in

the art can clearly conclude that as of the filing date the inventor had possession of the invention as now claimed.

Thus, the instant specification clearly meets the written description requirements with respect to the instant claimed invention and withdrawal of this rejection is respectfully requested.

III. Rejection of Claims 1, 15, 21 and 34 under 35 U.S.C. 102(b)

The rejection of claims 1, 15, 21 and 34 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,543,144 has been maintained. Arguments presented previously that Chang do not teach administering the nucleic acids to cells, but rather the antibodies to the cells were not found convincing as the Examiner suggests that intended use is not considered limiting in art rejections for composition claims.

Applicants respectfully traverse this rejection.

Chang (U.S. Patent 5,543,144) teaches methods of treating allergic reactions by reducing circulating IgE using antibodies which specifically bind to secreted IgE and membrane-bound IgE on the surface of IgE-producing B cells. The pharmaceutical composition according to Chang consists of a monoclonal antibody, or, as Chang proposes, the composition may consist of monoclonal antibody derivates,

such as for example recombinant single chain antibodies wherein the heavy and light chain variable domains are connected via a linker, as such derivates are well known in the art.

In contrast, methods of the present invention do not comprise delivery of an antibody composition. Instead, the present invention provides a method comprising delivery of a DNA construct.

In an earnest effort to advance the prosecution of this case, Applicants have amended the pending claims to be drawn to methods for passive immunisation of an animal against a disease-causing agent by administering to an animal non-infectious eukaryotic expression vector nucleic acid construct comprising a DNA sequence encoding a recombinant antibody molecule derived from an antibody raised against the disease-causing agent.

Since Chang et al. do not teach administration of a DNA construct, this reference cannot anticipate the invention as now claimed.

Withdrawal of this rejection under 35 U.S.C. 102(b) is therefore respectfully requested.

IV. Rejection of Claims 1-7, 9, 12-13, 16-18, 21-27, 31-32, 35-37, 44-48 and 50-54 under 35 U.S.C. 103(a)

Claims 1-7, 9, 12-13, 16-18, 21-27, 31-32, 35-37, 44-48 and 50-54 have been rejected under 35 U.S.C. 103(a) as being

unpatentable over Duan (WO 96/37234). The Examiner suggests that at the time of the invention by Applicant, it would have been obvious to one of skilled in the art to modify the compositions and methods of Duan to include the signal sequence of the antibody within the nucleic acids and to administer such compositions to patients. The Examiner suggests that the artisan would have been motivated to do so in order to obtain extracellular expression and protect against extracellular pathogens. Further, the Examiner suggests that the artisan would have had a reasonable expectation of success because these antibodies naturally included such signal sequences, and Duan was removing them in order to stop secretion.

Applicants respectfully traverse this rejection.

Duan's (WO96/3734) method for conducting gene therapy involves using a recombinant gene that encodes an antibody that binds an antigen associated with the disease and provides cells with "immunity" against a pathogen intracellularly. In the abstract (page 2, lines 27-29) Duan teaches that "the foregoing treatments (e.g.passive immunization) are limited in that the most active site for many diseases (e.g. HIV) is within the cell, beyond the reach of antibodies". Furthermore, it is stated (p.2 lines 29-32) that "synthetic antibodies (e.g.introduced to an

animal by passive immunization) have relatively short life, during which they are subject to serious proteolytic and other degradation". The method for conducting gene therapy taught by Duan is described as an improved method, wherein the improvement is that the "recombinant genes are prepared so as to be free of a signal sequence" (which is a sequence for secretion of the antibody) thereby maintaining the expressed synthetic antibodies within the cells. Thus, Duan actually teaches away from a construct encoding both a recombinant antibody against a disease-causing agent (e.g.HIV) and a signal sequence for secretion of the antibodies expressed within the cell.

Further, the Examiner's suggestion to include a signal sequence in the teachings of Duan changes completely the principal of operation of Duan and thus is improper in accordance with MPEP 2143.01. Also see In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) which holds that if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.

Applicants also respectfully disagree with the Examiner's characterization Duan (page 4 lines 6-18) as

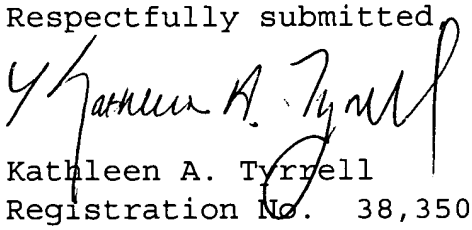
teaching use of a construct encoding a recombinant antibody in animals with deficient immune system. On p. 4 lines 6-18 of Duan it is stated that "in a particular preferred embodiment, the antibody gene is under control of a pathogen promoter which is expression dependent on the presence of a [pathogen] protein, so that intracellular expression of the antibody will not occur until the cell is also infected by a pathogen that can initiate the regulatory effects of that protein". The example of such pathogen is HIV. Thus, Duan's teaching concerns an organism which acquires immune deficiency e.g. following the infection with HIV, and the construct according to Duan remains "silent" until the organism become infected with a pathogen (e.g. HIV). This means that the construct according to Duan is not suitable for the purpose of prophylaxis of a disease by means of passive immunisation.

Accordingly, Duan provides neither the motivation or suggestion to modify its teachings to arrive at the present invention nor a teaching or suggestion of all the claim limitations as required by MPEP 2143 to render the instant invention obvious. Withdrawal of this rejection under 35 U.S.C. 103 is therefore respectfully requested.

V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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